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# **Evaluation of the Association between Persistent Organic Pollutants (POPs) and Diabetes in Epidemiological Studies: A National Toxicology Program Workshop Review**

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## **Contributors**

Raymond Novak served as chair and Kyla Taylor served as rapporteur for the POPs breakout group. The following authors were also members of the POPS breakout group: Henry Anderson, Linda Birnbaum, Chad Blystone, Abee Boyles, Mike DeVito, David Jacobs, Josef Köhrle, Duk-Hee Lee, Lars Lind, and Rogelio Tornero-Velez. Kristina Thayer assisted in preparing background materials for the workshop and writing the manuscript. Ana Rignell-Hydbom, Lars Rylander, and Mary Turyk, were not formal members of the breakout group but their contributions during the workshop deliberations and in follow-up discussions to assess the feasibility of conducting a meta-analysis or pooled analysis were significant enough to merit co-authorship.

## **Conflict of interest**

The authors declare they have no competing financial interests with respect to this manuscript, or its content, or subject matter.

## **Abbreviations**

BMI - body mass index

DDE - dichlorodiphenyldichloroethylene

DDT - dichlorodiphenyltrichloroethane

DDD - dichlorodiphenyldichloroethane

dL - decilitre

DNTP - Division of the National Toxicology Program

GLUT - glucose transporter

GLUT4 - glucose transporter type 4

HbA1c - hemoglobin A1c; glycosylated haemoglobin

HOMA-IR - homeostasis model assessment of insulin resistance

NHANES - National Health and Nutrition Examination Survey

OGGT - oral glucose tolerance test

OR - odds ratio

POPs - persistent organic pollutants

PBB - polybrominated biphenyls

PBDE - polybrominated diphenyl ethers

PCB - polychlorinated biphenyls

PCDD - polychlorinated dibenzodioxins

PCDF - polychlorinated dibenzofurans

PFAAs - perfluoroalkyl acids

PFOS - perfluorooctane sulfonate

PFOA - perfluorooctanoic acid

PFHxS - perfluorohexane sulfonate

PFNA - perfluorononanoic acid

SMR - standardized mortality ratio

T1D - type 1 diabetes

T2D - type 2 diabetes

TCDD - 2,3,7,8-tetrachlorodibenzodioxin

## **Abstract**

**Background:** Diabetes is a major threat to public health in the US and world-wide. Understanding the role of environmental chemicals in the development or progression of diabetes is an emerging issue in environmental health.

**Objective:** The objective of this evaluation is to assess the epidemiologic literature for evidence of associations between POPs and type 2 diabetes.

**Methods:** We identified 72 epidemiological studies investigating associations of POPs with diabetes from a PubMed search and reference lists of relevant studies or review articles. This literature was evaluated for consistency, strengths and weaknesses of study design (including power and statistical methods), clinical diagnosis, exposure assessment, and study population characteristics; and to identify data gaps and areas for future research.

**Conclusions:** Heterogeneity of the studies precluded conducting a meta-analysis, but the overall evidence is sufficient for a positive association of some organochlorine POPs with type 2 diabetes. Collectively, these data were not considered sufficient to establish causality. Initial data-mining revealed that the strongest positive correlation of diabetes with POPs occurred with organochlorine compounds, such as trans-nonachlor, DDE, PCBs, and dioxins/dioxin-like chemicals. There is less indication for an association with other non-organochlorine POPs, such as perfluoroalkyl acids (PFAAs) and brominated compounds. Experimental data are needed to confirm the causality of these findings which will shed a new light on the pathogenesis of diabetes with consequences for governmental bodies involved in the regulation of environmental contaminants.

## Introduction

Diabetes is a major threat to public health in the United States and worldwide (CDC 2011; Danaei et al. 2011; WHO 2011). Whereas Type 1 diabetes (T1D) is largely thought to be of an autoimmune origin, Type 2 diabetes (T2D) is mainly associated with obesity and metabolic syndrome, although cases of T2D can occur independently of being overweight or obese. Based on data from the 2005-2008 National Health and Nutrition Examination Survey (NHANES), 25.6 million, or 11.3%, of all people in the US aged  $\geq 20$  years are estimated to have diagnosed or undiagnosed diabetes, with associated direct medical costs and indirect costs (disability, work loss, premature death) of \$174 billion in 2007 alone. Another 35% of people  $\geq 20$  years of age are believed to be pre-diabetic, a condition where fasting blood glucose, blood glucose following a 2-hour oral glucose tolerance test (OGTT), or plasma HbA1c levels are above normal but not sufficiently elevated to be classified as diabetes (CDC 2011). The pre-diabetic condition often portends the subsequent development of T2D and is a risk factor for micro- and macrovascular diseases (Tabák et al. 2012).

Approximately 11% of prediabetic patients who participated in the Diabetes Prevention Program, a large multicenter randomized clinical trial developed by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), developed T2D each year during the average 3 years of follow-up (American Diabetes Association ; Knowler et al. 2002). Recently, T2D is being diagnosed in individuals earlier in life, including adolescents (NIDDK 2011). Given the number of people impacted by the disease, estimated to be 346 million worldwide (WHO 2011), and the long term consequences of diabetes in terms of morbidity, mortality, and economic costs, there is considerable interest in understanding the contribution of “non-traditional” risk factors, such as environmental chemicals, to the diabetes epidemic. Environmental exposures that have been

linked to diabetes in at least some study populations include persistent organic pollutants, arsenic, bisphenol A, phthalates, organotins, non-persistent pesticides (Thayer et al. 2012) and air pollution (Coogan et al. 2012; Hathout et al. 2006; Kramer et al. 2010; O'Neill et al. 2007; Pearson et al. 2010).

Research addressing the role of environmental chemicals in T2D has rapidly expanded in the past several years. The February 2011 Diabetes Strategic Plan from NIDDK (NIDDK 2011) acknowledges the growing science base in this area and cites the need to understand more about the role of environmental exposures as part of future research and prevention strategies. To help develop such a research strategy the National Toxicology Program (NTP) of the National Institute of Environmental Health Sciences (NIEHS) organized a state of the science workshop in January 2011 entitled “Role of Environmental Chemicals in the Development of Diabetes and Obesity” (National Toxicology Program 2011). The objective of this workshop was to examine the literature for evidence of associations between certain chemicals and obesity or diabetes. Epidemiological studies of associations between diabetes and persistent organic pollutants (POPs), particularly the halogenated POPs, were considered at the workshop, along with studies of diabetes in association with arsenic, maternal smoking during pregnancy, bisphenol A, phthalates, organotins, and non-persistent pesticides (Thayer et al. 2012). A wide variety of chemicals were included in the POPs category, including organochlorines [2,3,7,8-tetrachlorodibenzodioxin (TCDD or dioxin), Agent Orange, other non-TCDD polychlorinated dibenzo-p-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), polychlorinated biphenyls (PCBs), dichlorodiphenyltrichloroethane (DDT), dichlorodiphenyldichloroethylene (DDE), and dichlorodiphenyldichloroethane (DDD)]; brominated compounds [polybrominated diphenyl ethers (PBDEs) and polybrominated biphenyls (PBBs)]; and perfluorinated compounds



[perfluorooctane sulfonate (PFOS), perfluorooctanoic acid (PFOA), perfluorohexane sulfonate (PFHxS), and perfluorononanoic acid (PFNA)].

For the present review we evaluated the literature in terms of consistency, strengths, and weaknesses (including power and statistical methods) of the clinical diagnosis, exposure assessment, and study population characteristics, and to identify data gaps and areas for future evaluation/research in the area of POPs exposure and diabetes outcomes.

## **Methods**

### **Literature Search**

We developed a PubMed MeSH-based and a keyword search strategy to identify epidemiological studies of POPs exposure (organochlorine, organofluorine, and organobromine compounds) and health outcomes related to T1D, T2D, and childhood obesity (see Supplemental Material, page 3, for detailed information on the literature search strategy). We conducted an initial search on August 24, 2009 and subsequently updated it through December 15, 2010. Both adult and children's studies of POPs and T2D or diabetes-related outcomes (e.g. metabolic syndrome) were eligible for review. We excluded studies from consideration if they were occupational, used death certificates to identify T2D, or did not present original data. Due to time constraints we only formally assessed studies with T2D as the outcome, excluding studies with metabolic syndrome as the outcome in our evaluation. After removal of duplicates, our search identified a total of 2,752 publications, 72 of which presented original data on diabetes-related studies (see Supplemental Materials, Figure S1). We excluded 28 studies from consideration because the health outcome was not T2D or the method used to measure exposure or classify T2D was not considered adequate (see Supplemental Table S1). We considered blood or target tissue levels

the most informative exposure measures, however this information was not always available (e.g. studies of Vietnam Veterans). Vietnam Veteran studies that were excluded were not specific enough to infer exposure to Agent Orange or TCDD (e.g. veterans who were in Vietnam vs veterans who were not in Vietnam. This was not specific enough to accept as exposed vs. not exposed. We did not consider occupational studies in this particular workshop because exposure may be more targeted depending on the occupation. Similarly we also did not consider a study by Anderson-Mahoney et al (2008) because the population studied were plaintiffs involved in a lawsuit due to unusually high levels of exposure in drinking water. Also potential biases that are unique to these studies, such as the healthy worker effect, may be introduced. We excluded studies that used death certificates to identify diabetes cases because the prevalence of diabetes is known to be underestimated from mortality data. For example, diabetes was listed as a direct or contributing cause of death on only 6.2% of the death certificates for adults who were known to have diabetes in a U.S.-based study which characterized the sensitivity and specificity of death certificates for diabetes (Cheng et al. 2008).

We identified an additional 17 articles by reviewing the reference lists in the primary literature and review articles, for a total of 43 studies.

### **Data Extraction**

NTP OHAT staff extracted the main findings from the included studies (see Supplemental Material, Table S2). The identification of the main findings was based on the following strategy: when a study did not report a statistically significant association,  $p\text{-value} > 0.05$ , between POPs exposure and T2D at any exposure level we extracted the main finding from the highest exposure group compared to the referent group (e.g., 4<sup>th</sup> quartile versus 1<sup>st</sup> quartile); when a study reported a statistically significant association between POPs exposure and T2D, and that association

displayed a monotonic dose response, we extracted the main finding based on the lowest exposure group with a statistically significant association (e.g., 3<sup>rd</sup> quartile versus 1<sup>st</sup> quartile); when associations were non-monotonic in nature we identified the main findings on a case by case basis and considered any statistical trend analyses that might have been conducted, consistency of the overall pattern across exposure groups, and/or the biological significance of the non-monotonic finding.

As noted above, POPs represent a toxicologically diverse range of chemicals that all have the common feature of being persistent in the body (i.e., long half-life) and the environment. Chemicals are broadly divided into categories based on the halogen group (chlorinated, fluorinated, brominated). Within the chlorinated group we further divided chemicals into common chemical class designations used in toxicology, i.e, dioxins, PCBs, DDT/DDE/DDD. In assessing the PCB studies we evaluated total PCBs and PCB153 together because PCB153 is a major contributor to total PCB exposure and is used as an indicator PCB. PCB153 is often used as a surrogate measure for total PCBs because it is less expensive to measure (Cote et al. 2006; Meeker and Hauser 2010). Assessing patterns of association across studies of individual PCBs is particularly challenging because the class contains 209 structures that are not easy to categorize based on structural similarity and/or biological activity. Even the categorization of “dioxin-like” or “non-dioxin like” is not considered sufficient since both categories of PCBs are linked to diabetes (Giesy and Kannan 1998; Lee et al. 2010; Lee et al. 2006; Lee et al. 2011a). In general, the findings for individual PCB congeners other than PCB153 are less suggestive for an overall association (see Supplemental Materials, Figure S2) (Codru et al. 2007; Everett et al. 2007; Lee et al. 2010; Patel et al. 2010; Turyk et al. 2009a).

## **Study Quality**

We categorized studies into several groups based on study design and nature of the exposure: (1) cohort studies with a prospective or nested case-control design, (2) cross sectional studies, (3) case-control studies, (4) occupational studies, (5) ecological studies, (6) studies of maternal exposure, and (7) studies of Vietnam veterans.

We included a study for consideration if it identified T2D as the outcome and the exposure measure was deemed adequate (see Literature Search). The panel members judged the study to be of sufficient quality during workshop deliberations. Aspects of study quality included potential selection bias, possibility of association being due to reverse causation, or loss to follow-up. These were not summarized for each study but were considered during discussion.

## **Use of Meta Data Viewer to Assess Patterns of Findings**

The POPs literature on diabetes is quite complex consisting of 72 epidemiological studies that often report findings for multiple compounds in the same study. To visually assess patterns of primary study findings from this literature we used a newly developed software program referred to as the Metadata Viewer (Boyles et al. 2011). In brief, the Meta Data Viewer is a graphing program that can display up to 15 text columns and graph 1 to 10 numerical values. The input data file is an Excel document, and users can sort, group, and filter data to look at patterns of findings across studies. We used this software program to visually display data during the workshop and to generate the figures published in this report. The odds ratios (ORs) and 95% confidence intervals (CIs) were displayed in the figures as reported by the study's authors; in some cases rounding may affect the appearance of symmetry for the 95% confidence intervals. The graphing program, accompanying data file, and instructions for use are publicly accessible at [http://ntp.niehs.nih.gov/go/tools\\_metadataviewer](http://ntp.niehs.nih.gov/go/tools_metadataviewer) (Boyles et al. 2011). The data file currently

contains 870 main findings from over 200 human studies on diabetes- and childhood obesity-related outcomes for POPs, as well as other exposures, including metals (arsenic, cadmium, lead, mercury, etc.), bisphenol A, non-persistent pesticides, phthalates, and maternal smoking during pregnancy. Meta Data Viewer is a public resource and users are welcome to use the program and any associated NTP data files for their own purposes, including for use in publications. Assistance in using the data file and software program is available upon request at the URL above.

## **Main Findings**

We took into account patterns of findings for chemicals or chemical classes if at least three different studies reported diabetes-related outcomes for that chemical or chemical class. We did not consider the epidemiological evidence sufficient to determine whether any of the positive associations were causal in nature.

The strongest positive associations were with trans-nonachlor (Figure 1), DDE, DDT, and DDD (Figure 2), dioxins/dioxin-like chemicals and certain PCBs (Figure 3), and Agent Orange or 2,3,7,8-tetrachlorodibenzodioxin (TCDD) in Vietnam veterans (Figure 4). Findings from studies of trans-nonachlor (Airaksinen et al. 2011; Lee et al. 2011a), DDE (Airaksinen et al. 2011; Grandjean et al. 2011; Lee et al. 2011a) and PCBs (Grandjean et al. 2011; Lee et al. 2011a; Persky et al. 2011) published after the workshop are consistent with the conclusions reached during the workshop (see Supplemental Material, Figures S2 and S3).

Among specific organochlorine chemicals that were evaluated in < 6 studies, including dieldrin, hexachlorobenzene (HCB),  $\beta$ -hexachlorocyclohexane ( $\beta$ HCH), lindane ( $\gamma$ HCH), heptachlor

epoxide, mirex, and oxychlordane, we found positive patterns of associations (Figure 5). However, in many cases the estimates of association reported by individual studies were not statistically significant (Chen et al. 2006; Codru et al. 2007; Cox et al. 2007; Everett et al. 2007; Everett and Matheson 2010; Lee et al. 2010; Lee et al. 2006; Michalek and Pavuk 2008; Patel et al. 2010; Son et al. 2010; Steenland et al. 2001; Sweeney et al. 1997; Uemura et al. 2008; Ukropec et al. 2010). Similarly, an overall pattern of a positive association was apparent in studies of mixtures of organochlorine POPs (Jorgensen et al. 2008; Lee et al. 2010; Lee et al. 2006; Ukropec et al. 2010) (Figure 6).

Overall we found that organochlorine compounds are positively associated with diabetes. Workshop participants concluded that there was not sufficient evidence for an association between T2D and polybrominated biphenyls (PBBs) or polybrominated diphenyl ethers (PBDEs) (Lee et al. 2010; Lim et al. 2008; Turyk et al. 2009b; Vasiliu et al. 2006) (Figure 7). Results from studies published after the workshop examining an association between T2D and PBDE153 and PBDE47 are consistent with this initial assessment (Airaksinen et al. 2011; Lee et al. 2011a) (see also Supplemental Material, Figure S2). Workshop participants also concluded that there was not sufficient evidence for an association between T2D and perfluoroalkyl acids (PFAAs) such as perfluorooctanyl sulfonate (PFOS) and perfluorooctanoic acid (PFOA) (Costa et al. 2009; Lin et al. 2009; MacNeil et al. 2009; Melzer et al. 2010; Nelson et al. 2010) (Figure 8).

## **Discussion**

The purpose of this evaluation was not only to assess the epidemiologic literature for evidence of associations between POPs and T2D, but to collaboratively identify data gaps and areas for future research in the area of POPs exposure and outcomes related to diabetes. It is important to

note that this list includes topics that are related to but not specifically discussed in this evaluation. For example, there was only one epidemiological study on POPs and T1D, a very important health outcome (Rignell-Hydbom et al. 2010). The full list of data gaps and research needs that were recommended by workshop participants based on this review are summarized in Appendix 1.

### **Vietnam Veteran Studies**

The conclusion from this evaluation, that there is an association with diabetes in Vietnam veterans, differs somewhat from assessments conducted by the Institute of Medicine (IOM) Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides. The evidence for an association between exposure to herbicides used during the Vietnam War and long-term health effects in veterans, including diabetes, is assessed every other year by this committee as part of the Agent Orange Act of 1991. The strength-of-evidence conclusion from the epidemiological studies included in the first report, published in 1994, was for “inadequate or insufficient evidence to determine whether an association exists between exposure to herbicides [2,4-dichlorophenoxyacetic acid (2,4-D), 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) and its contaminant TCDD; cacodylic acid; and Picloram] and diabetes mellitus.” (Institute of Medicine (IOM) 1994). However, a committee convened by the IOM in 1999 to conduct a specific review of the scientific evidence regarding T2D and Agent Orange in Vietnam veterans concluded that there was “limited/suggestive evidence” of an association between T2D and exposure to Agent Orange used in Vietnam (Institute of Medicine (IOM) 2001). This conclusion was maintained in *The Veterans and Agent Orange: Update* in 2001, 2002, 2004, 2006, 2008, and 2010 (Institute of Medicine (IOM) 2011). In contrast, the conclusion from the present evaluation was that there was evidence for a “positive” association when the data were looked at collectively (Figure 4).

## **Risk Factors and Confounding**

Epidemiological studies regarding POPs and diabetes and other metabolic disorders should consider gender, age, race/ethnicity, and combinations of exposures with other agents (e.g., plastic associated compounds, such as bisphenol A, and metals) as potential confounding or modifying variables.

It is less clear whether studies should use lipid standardized blood measurement for lipophilic chemicals and a variety of approaches are currently used: ranging from presentation of 1) wet concentrations without consideration of lipid profiles, 2) lipid-standardized concentrations, or 3) wet concentrations with lipid adjustments in the models. As POPs move with serum lipids, high blood lipids increase measured levels of POPs. Therefore, the failure to account for this relation may result in overestimation of relative risks. However, the exposure to certain chlorinated POPs can lead to increased levels of serum lipids and dyslipidemia is involved in the pathogenesis of T2D, suggesting that dyslipidemia can be seen as an intermediate factor in the relation between POPs and T2D. In this situation, adjusting for this relation may underestimate true associations. Even though true associations may be somewhere between unadjusted and adjusted results, there is uncertainty about the most appropriate way to deal with lipids.

Adjusting for obesity is controversial when studying the association between POPs and diabetes. There is growing evidence that obesity is on the causal pathway between POPs and diabetes (Lee et al. 2011b; Ruzzin et al. 2010). In addition, this relationship is potentially confounded by fatty food consumption as it is well-recognized that this variable causes both obesity and increased POPs levels. However, adipose tissue serves as a reservoir of POPs thereby reducing the circulating levels of POPs (Lim et al. 2010). This effect might have a positive role in limiting the exposure to target tissues for diabetes, such as pancreatic beta-cells.



### **Non-monotonic exposure-response relationships**

Several studies reported evidence of non-monotonic exposure response relationships in this literature. For example, in the CARDIA cohort, estimated associations with diabetes were strongest for the 2<sup>nd</sup> quartiles of exposure to trans-nonachlor, oxychlordane, mirex, highly chlorinated PCBs, and PBB153 (Lee et al. 2010). Even though other studies (Lee et al. 2011a; Rignell-Hydbom et al. 2009; Turyk et al. 2009a) tend to report monotonic relationships, a closer evaluation of the dose-response curves from each study revealed that the risk of diabetes was substantially increased with only small increases within lower ranges of POPs concentrations, but only slightly increased with higher increases in concentrations of POPs. For example, in the PIVUS study, the adjusted ORs across quintiles of summary measure of PCBs were 1.0, 4.5, 5.1, 8.8, and 7.5 (Lee et al. 2011b).

In this sense, the dose-response curves presented in these studies share the low dose portion of a wide inverted U-shaped association. Varying background exposure distributions may contribute to different forms of the concentration-response curves seen between studies, depending on the relative importance of different POPs in the background mixture. The inverted U-shaped association has been suspected to be biologically linked to the endocrine disrupting properties of POPs in that an increase from no to low occupancy of hormone receptors has been observed to have linear effects on hormone mediated phenomena, but that effect sometimes decelerates or even stops when dose gets higher (Vandenberg et al. 2012). Improving understanding of the biological basis for potential non-linear relationships was considered an important research need (Appendix 1).

### **Meta-analysis or pooled analysis of existing studies**

Workshop participants discussed the possibility of conducting a meta-analysis of existing studies, or a pooled analysis of individual-level data from prospective studies, in particular the five prospective studies of PCB153 and DDE (Lee et al. 2010; Lee et al. 2011a; Rignell-Hydbom et al. 2009; Turyk et al. 2009a; Vasiliu et al. 2006), but participants concluded that there was too much variation across studies to permit a meta- or pooled analysis. For example, the five studies of PCB153 and DDE used different diagnostic strategies and different approaches to address confounding, particularly by serum lipid levels (Lee et al. 2010). The cohorts also varied with regard to age, from 18 to 30 years (Lee et al. 2010) to 70 years (Lee et al. 2011a), and gender, which was exclusively female in one study (Rignell-Hydbom et al. 2009), exclusively male in another (Lee et al. 2010), and mixed in the remaining cohorts (Lee et al. 2011a; Turyk et al. 2009a; Vasiliu et al. 2006). In addition, temporal and geographic variation among the cohorts resulted in substantial differences in the chemical mixtures to which the populations were exposed, and the duration and relative concentrations of exposures.

### **Causality**

Although a number of organochlorine compounds show positive associations with T2D we can not determine if these associations are causal in nature based on observational epidemiologic studies alone, and additional animal and *in vitro* mechanistic studies are needed to clarify the role of POPs in metabolic disease development. Factors to be considered in such studies should address the influence of time windows of exposure; exposure measurements (e.g., the chemical analysis of individual POPs); chemical mixtures identifying relevant tissue targets; biological mechanisms that lead to obesity, insulin resistance, lipidemia, and diabetes; and the influence of genetic variation among animal models. Combining results from relevant mechanistic and animal

studies with findings from epidemiologic studies would enhance our ability to establish a possible causal linkage between POPs and diabetes.

Identification of individual chemicals or chemical mixtures that are associated with T2D in epidemiology studies will help direct further toxicity testing. In concert, toxicity testing or screening of chemical classes using assays relevant to diabetes will also help epidemiologists determine which chemicals to measure in future studies. The structures of chemicals that are associated with diabetes are highly variable and it is difficult to link them to a common etiologic mechanism. Further research to identify all relevant pathways to diabetes will aid in deciphering structure activity relationships.

While this evaluation focused on the epidemiological data, findings from *in vitro* and animal data show that TCDD, PCBs, and other chlorinated POPs can cause pancreatic effects (Ebner et al. 1993; Rao et al. 1988; Rozman et al. 1986; Wassermann et al. 1975), and influence insulin signalling (Ibrahim et al. 2011; Kim et al. 2009; Nishiumi et al. 2010; Ruzzin et al. 2010; Tang et al. 2007; Wang et al. 2010), glucose-stimulated insulin secretion (Fischer et al. 1999; Hsu et al. 2010a; Kurita et al. 2009; Novelli et al. 2005; Piaggi et al. 2007), glucose uptake (Enan et al. 1992a, b; Olsen et al. 1994), gluconeogenesis (Boll et al. 1998; Gorski et al. 1990; Viluksela et al. 1999), and adipocyte differentiation or regulation (Arsenescu et al. 2008; Hsu et al. 2010b; Mullerova and Kopecky 2007; Shimba et al. 2001).

However, the laboratory animal data on organochlorine-induced changes in glucose and insulin levels are not necessarily consistent with associations between POPs and an increased incidence of T2D reported by epidemiologic studies. It is unclear whether the lack of consistency can be accounted for by physiological differences between rodents and humans for diabetes, or

experimental variables related to differences in exposure levels, the window of exposure, and/or the duration of exposure and length of follow up. Much of the work in this area is based on TCDD exposure. In humans, diabetes is characterized by increased blood glucose levels. In contrast, in different animal models, TCDD has been shown to cause hypoglycemia (Fried et al. 2010; Gorski and Rozman 1987; Viluksela et al. 1998; Viluksela et al. 1999), to have no effect on glucose levels (Unkila et al. 1995), or to cause both hyper- and hypoglycemia at different time points during or following dosing (Ebner et al. 1988; Potter et al. 1983). Also, while epidemiology studies tend to show a positive relationship between TCDD body burdens and insulin levels (Cranmer et al. 2000; Michalek et al. 1999), TCDD typically causes hypoinsulinemia and increased insulin sensitivity in animals (Ebner et al. 1988; Fried et al. 2010; Gorski et al. 1988; Gorski and Rozman 1987; Potter et al. 1983; Stahl et al. 1992; Weber et al. 1987). Thus, in animal models, exposure to TCDD mimics the feature of reduced insulin secretion observed in the clinical progression of pre-diabetes to overt diabetes. Inhibition of glucose uptake may at least partially explain why hypoinsulinemia is frequently observed in animal studies. In most tissues studied, TCDD inhibits glucose uptake by decreasing the activity or protein level of glucose transporter (GLUT) proteins responsible for transporting blood glucose to adipose, muscle, pancreas, liver, and intestinal epithelium tissue (El-Sabeawy et al. 2001; Enan et al. 1992b; Liu and Matsumura 1995; Matsumura 1995; Olsen et al. 1994). Decreased glucose uptake into the pancreas could mean that pancreatic  $\beta$  cells are not sensing higher blood glucose levels and therefore not eliciting an insulin response to those levels (Matsumura 1995). The level of glucose uptake inhibition appears to correlate with the activation of the aryl hydrocarbon (Ah) receptor which is required for TCDD-induced toxicological effects (Matsumura 1995; Olsen et al. 1994). However, the dioxin exposures in these *in vivo* and *in vitro*

studies are approximately 1,000 to 100,000 times background body burdens observed in the US population. The *in vivo* studies are associated with body weight loss, histopathological findings, and significant decreases in thyroid hormones. Extrapolating these effects and mechanisms to background human exposures is challenging.

## **Conclusions**

Diabetes is a major threat to public health worldwide (WHO 2011), and although there are well-established risk factors for diabetes, such as excess weight, environmental chemicals might also contribute to the etiology of this disease. Based on human epidemiological studies we conclude that there is support for positive associations between diabetes and certain chlorinated POPs. We identified a number of research needs (Appendix 1), noting in particular the need to (1) better understand the relationships between both developmental and adult exposure to POPs and obesity, diabetes, and related metabolic disturbances; (2) identify mechanisms for the observed associations, which will require basic research to develop better animal models and identify relevant biological pathways that could be assessed using *in vitro* screening systems; (3) understand the modifying effects of factors such as inflammation, visceral fat, other chemical exposures, genotype, age at exposure, and the duration of exposure; and (4) develop improved methods to measure POPs in small blood volumes using high throughput technologies at a reasonable cost.

Type 2 Diabetes is a debilitating disease that affects adults as well as children and adolescents. The economic impact of the disease, not only in terms of direct medical costs, but also on lost productivity, is enormous. Therefore, understanding the impact of environmental factors, such as chemical exposures, is a high priority research goal (NIDDK 2011). Hence, exposure to

environmental chemicals may be an additional risk factor that, if prevented, could facilitate a reduction in disease incidence and the overall associated health and economic burden.

## References

- Airaksinen R, Rantakokko P, Eriksson JG, Blomstedt P, Kajantie E, Kiviranta H. 2011. Association Between Type 2 Diabetes and Exposure to Persistent Organic Pollutants. *Diabetes Care* 34(9):1972-1979.
- American Diabetes Association. Prediabetes FAQs (<http://www.diabetes.org/diabetes-basics/prevention/pre-diabetes/pre-diabetes-faqs.html>) [accessed 8 December 2011].
- Anderson-Mahoney P, Kotlerman J, Takhar H, Gray D, Dahlgren J. 2008. Self-reported health effects among community residents exposed to perfluorooctanoate. *New Solut* 18(2):129-143.
- Arsenescu V, Arsenescu RI, King V, Swanson H, Cassis LA. 2008. Polychlorinated biphenyl-77 induces adipocyte differentiation and proinflammatory adipokines and promotes obesity and atherosclerosis. *Environ Health Perspect* 116(6):761-768.
- Boll M, Weber LW, Messner B, Stampfl A. 1998. Polychlorinated biphenyls affect the activities of gluconeogenic and lipogenic enzymes in rat liver: is there an interference with regulatory hormone actions? *Xenobiotica* 28(5):479-492.
- Boyles AL, Harris SF, Rooney AA, Thayer KA. 2011. Forest Plot Viewer: a fast, flexible graphing tool. *Epidemiol* 22(5):746-747.
- CDC. 2011. National Diabetes Fact Sheet, Data and Trends. <http://apps.nccd.cdc.gov/DDTSTRS/default.aspx> [accessed 12 December 2011].
- Chen HL, Su HJ, Guo YL, Liao PC, Hung CF, Lee CC. 2006. Biochemistry examinations and health disorder evaluation of Taiwanese living near incinerators and with low serum PCDD/Fs levels. *Sci Total Environ* 366(2-3):538-548.
- Cheng WS, Wingard DL, Kritz-Silverstein D, Barrett-Connor E. 2008. Sensitivity and specificity of death certificates for diabetes: as good as it gets? *Diabetes Care* 31(2):279-284.
- Codru N, Schymura MJ, Negoita S, Rej R, Carpenter DO. 2007. Diabetes in relation to serum levels of polychlorinated biphenyls and chlorinated pesticides in adult Native Americans. *Environ Health Perspect* 115(10):1442-1447.
- Coogan PF, White LF, Jerrett M, Brook RD, Su JG, Seto E, et al. 2012. Air Pollution and Incidence of Hypertension and Diabetes in African American Women Living in Los Angeles. *Circulation*.

- Costa G, Sartori S, Consonni D. 2009. Thirty years of medical surveillance in perfluooctanoic acid production workers. *J Occup Environ Med* 51(3):364-372.
- Cote S, Ayotte P, Dodin S, Blanchet C, Mulvad G, Petersen H, et al. 2006. Plasma organochlorine concentrations and bone ultrasound measurements: a cross-sectional study in peri-and postmenopausal Inuit women from Greenland. *Environmental Health: A Global Access Science Source* 5(1):33.
- Cox S, Niskar AS, Narayan KM, Marcus M. 2007. Prevalence of self-reported diabetes and exposure to organochlorine pesticides among Mexican Americans: Hispanic health and nutrition examination survey, 1982-1984. *Environ Health Perspect* 115(12):1747-1752.
- Cranmer M, Louie S, Kennedy RH, Kern PA, Fonseca VA. 2000. Exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) is associated with hyperinsulinemia and insulin resistance. *Toxicol Sci* 56(2):431-436.
- Danaei G, Finucane MM, Lu Y, Singh GM, Cowan MJ, Paciorek CJ, et al. 2011. National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2.7 million participants. *Lancet* 378(9785):31-40.
- Ebner K, Brewster DW, Matsumura F. 1988. Effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin on serum insulin and glucose levels in the rabbit. *J Environ Sci Health B* 23(5):427-438.
- Ebner K, Matsumura F, Enan E, Olsen H. 1993. 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) alters pancreatic membrane tyrosine phosphorylation following acute treatment. *Journal of Biochemical Toxicology* 8(2):71-81.
- El-Sabeawy F, Enan E, Lasley B. 2001. Biochemical and toxic effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin in immature male and female chickens. *Comparative Biochemistry and Physiology Toxicology & Pharmacology: CBP* 129(4):317-327.
- Enan E, Liu PC, Matsumura F. 1992a. 2,3,7,8-Tetrachlorodibenzo-p-dioxin causes reduction of glucose transporting activities in the plasma membranes of adipose tissue and pancreas from the guinea pig. *J Biol Chem* 267(28):19785-19791.
- Enan E, Liu PC, Matsumura F. 1992b. TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin) causes reduction in glucose uptake through glucose transporters on the plasma membrane of the guinea pig adipocyte. *J Environ Sci Health B* 27(5):495-510.



- Everett CJ, Frithsen IL, Diaz VA, Koopman RJ, Simpson WM, Jr., Mainous AG, 3rd. 2007. Association of a polychlorinated dibenzo-p-dioxin, a polychlorinated biphenyl, and DDT with diabetes in the 1999-2002 National Health and Nutrition Examination Survey. *Environ Res* 103(3):413-418.
- Everett CJ, Matheson EM. 2010. Biomarkers of pesticide exposure and diabetes in the 1999-2004 national health and nutrition examination survey. *Environ Int* 36(4):398-401.
- Fischer LJ, Wagner MA, Madhukar BV. 1999. Potential involvement of calcium, CaM kinase II, and MAP kinases in PCB-stimulated insulin release from RINm5F cells. *Toxicol Appl Pharmacol* 159(3):194-203.
- Fried KW, Guo GL, Esterly N, Kong B, Rozman KK. 2010. 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) reverses hyperglycemia in a type II diabetes mellitus rat model by a mechanism unrelated to PPAR gamma. *Drug Chem Toxicol* 33(3):261-268.
- Giesy JP, Kannan K. 1998. Dioxin-Like and Non-Dioxin-Like Toxic Effects of Polychlorinated Biphenyls (PCBs): Implications For Risk Assessment. *Critical Reviews in Toxicology* 28(6):511-569.
- Gorski JR, Muzi G, Weber LW, Pereira DW, Arceo RJ, Iatropoulos MJ, et al. 1988. Some endocrine and morphological aspects of the acute toxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). *Toxicologic pathology* 16(3):313-320.
- Gorski JR, Rozman K. 1987. Dose-response and time course of hypothyroxinemia and hypoinsulinemia and characterization of insulin hypersensitivity in 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)-treated rats. *Toxicology* 44(3):297-307.
- Gorski JR, Weber LW, Rozman K. 1990. Reduced gluconeogenesis in 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)-treated rats. *Arch Toxicol* 64(1):66-71.
- Grandjean P, Henriksen JE, Choi AL, Petersen MS, Dalgard C, Nielsen F, et al. 2011. Marine food pollutants as a risk factor for hypoinsulinemia and type 2 diabetes. *Epidemiology* 22(3):410-417.
- Hathout EH, Beeson WL, Ischander M, Rao R, Mace JW. 2006. Air pollution and type 1 diabetes in children. *Pediatr Diabetes* 7(2):81-87.
- Hsu HF, Tsou TC, Chao HR, Kuo YT, Tsai FY, Yeh SC. 2010a. Effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin on adipogenic differentiation and insulin-induced glucose uptake in 3T3-L1 cells. *J Hazard Mater* 182(1-3):649-655.

- Hsu HF, Tsou TC, Chao HR, Kuo YT, Tsai FY, Yeh SC. 2010b. Effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin on adipogenic differentiation and insulin-induced glucose uptake in 3T3-L1 cells. *Journal of hazardous materials* 182(1-3):649-655.
- Ibrahim MM, Fjaere E, Lock EJ, Naville D, Amlund H, Meugnier E, et al. 2011. Chronic consumption of farmed salmon containing persistent organic pollutants causes insulin resistance and obesity in mice. *PloS one* 6(9):e25170.
- Institute of Medicine (IOM). 1994. *Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam*. Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides; Institute of Medicine. Washington, DC: The National Academies Press.
- Institute of Medicine (IOM). 2001. *Veterans and Agent Orange: Update 2000*. The National Academies Press.
- Institute of Medicine (IOM). 2011. *Veterans and Agent Orange: Update 2010*. Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides (Eighth Biennial Update); Institute of Medicine. Washington, DC: The National Academies Press.  
[http://www.nap.edu/openbook.php?record\\_id=13166&page=705](http://www.nap.edu/openbook.php?record_id=13166&page=705) [accessed 14 January 2012].
- Jorgensen ME, Borch-Johnsen K, Bjerregaard P. 2008. A cross-sectional study of the association between persistent organic pollutants and glucose intolerance among Greenland Inuit. *Diabetologia* 51(8):1416-1422.
- Kim YH, Shim YJ, Shin YJ, Sul D, Lee E, Min BH. 2009. 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) induces calcium influx through T-type calcium channel and enhances lysosomal exocytosis and insulin secretion in INS-1 cells. *Int J Toxicol* 28(3):151-161.
- Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, et al. 2002. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med.* 346(6):393-403.
- Kramer U, Herder C, Sugiri D, Strassburger K, Schikowski T, Ranft U, et al. 2010. Traffic-related Air Pollution and Incident Type 2 Diabetes: Results from the SALIA Cohort Study. *Environ Health Perspect.*
- Kurita H, Yoshioka W, Nishimura N, Kubota N, Kadowaki T, Tohyama C. 2009. Aryl hydrocarbon receptor-mediated effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin on glucose-stimulated insulin secretion in mice. *J Appl Toxicol* 29(8):689-694.

- Lee D-H, Steffes MW, Sjodin A, Jones RS, Needham LL, Jacobs JDR. 2010. Low dose of some persistent organic pollutants predicts type 2 diabetes: A nested case-control study. *Environ Health Perspect* 118(9):1235-1242.
- Lee DH, Lee IK, Song K, Steffes M, Toscano W, Baker BA, et al. 2006. A strong dose-response relation between serum concentrations of persistent organic pollutants and diabetes: results from the National Health and Examination Survey 1999-2002. *Diabetes Care* 29(7):1638-1644.
- Lee DH, Lind PM, Jacobs DR, Jr., Salihovic S, van Bavel B, Lind L. 2011a. Polychlorinated biphenyls and organochlorine pesticides in plasma predict development of type 2 diabetes in the elderly: The Prospective Investigation of the vasculature in Uppsala Seniors (PIVUS) study. *Diabetes Care* 34(8):1778-1784.
- Lee DH, Steffes MW, Sjodin A, Jones RS, Needham LL, Jacobs DR, Jr. 2011b. Low dose organochlorine pesticides and polychlorinated biphenyls predict obesity, dyslipidemia, and insulin resistance among people free of diabetes. *PloS one* 6(1):e15977.
- Lim JS, Lee DH, Jacobs DR, Jr. 2008. Association of brominated flame retardants with diabetes and metabolic syndrome in the U.S. population, 2003-2004. *Diabetes Care* 31(9):1802-1807.
- Lim JS, Son HK, Park SK, Jacobs DR, Jr., Lee DH. 2010. Inverse associations between long-term weight change and serum concentrations of persistent organic pollutants. *International journal of obesity* (2005).
- Lin CY, Chen PC, Lin YC, Lin LY. 2009. Association among serum perfluoroalkyl chemicals, glucose homeostasis, and metabolic syndrome in adolescents and adults. *Diabetes Care* 32(4):702-707.
- Liu PC, Matsumura F. 1995. Differential effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin on the "adipose- type" and "brain-type" glucose transporters in mice. *Mol Pharmacol* 47(1):65-73.
- MacNeil J, Steenland NK, Shankar A, Ducatman A. 2009. A cross-sectional analysis of type II diabetes in a community with exposure to perfluorooctanoic acid (PFOA). *Environ Res* 109(8):997-1003.
- Matsumura F. 1995. Mechanism of action of dioxin-type chemicals, pesticides, and other xenobiotics affecting nutritional indexes. *The American Journal of Clinical Nutrition* 61(3 Suppl):695S-701S.

- Meeker JD, Hauser R. 2010. Exposure to Polychlorinated Biphenyls (PCBs) and Male Reproduction. *Systems Biology in Reproductive Medicine* 56(2):122-131.
- Melzer D, Rice N, Depledge MH, Henley WE, Galloway TS. 2010. Association between serum perfluorooctanoic acid (PFOA) and thyroid disease in the U.S. National Health and Nutrition Examination Survey. *Environ Health Perspect* 118(5):686-692.
- Michalek JE, Akhtar FZ, Kiel JL. 1999. Serum dioxin, insulin, fasting glucose, and sex hormone-binding globulin in veterans of Operation Ranch Hand. *J Clin Endocrinol Metab* 84(5):1540-1543.
- Michalek JE, Pavuk M. 2008. Diabetes and cancer in veterans of Operation Ranch Hand after adjustment for calendar period, days of spraying, and time spent in Southeast Asia. *J Occup Environ Med* 50(3):330-340.
- Mullerova D, Kopecky J. 2007. White adipose tissue: storage and effector site for environmental pollutants. *Physiol Res* 56(4):375-381.
- National Toxicology Program. 2011. "Role of Environmental Chemicals in the Development of Diabetes and Obesity" workshop. <http://ntp.niehs.nih.gov/go/36433> [accessed 8 November 2012].
- Nelson J, Hatch E, Webster T. 2010. Exposure to polyfluoroalkyl chemicals and cholesterol, body weight, and insulin resistance in the general U.S. population. *Environ Health Perspect* 118(2):197-202.
- NIDDK. 2011. Diabetes Research Strategic Plan. <http://www2.niddk.nih.gov/AboutNIDDK/ReportsAndStrategicPlanning/DiabetesPlan/PlanPosting.htm> [accessed 12 December 2011].
- Nishiumi S, Yoshida M, Azuma T, Yoshida KI, Ashida H. 2010. 2,3,7,8-Tetrachlorodibenzo-p-dioxin impairs an insulin signaling pathway through the induction of tumor necrosis factor {alpha} in adipocytes. *Toxicol Sci* 115(2):482-491.
- Novelli M, Piaggi S, De Tata V. 2005. 2,3,7,8-Tetrachlorodibenzo-p-dioxin-induced impairment of glucose-stimulated insulin secretion in isolated rat pancreatic islets. *Toxicol Lett* 156(2):307-314.
- O'Neill MS, Veves A, Sarnat JA, Zanobetti A, Gold DR, Economides PA, et al. 2007. Air pollution and inflammation in type 2 diabetes: a mechanism for susceptibility. *Occupational and Environmental Medicine* 64(6):373-379.

- Olsen H, Enan E, Matsumura F. 1994. Regulation of glucose transport in the NIH 3T3 L1 preadipocyte cell line by TCDD. *Environ Health Perspect* 102(5):454-458.
- Patel CJ, Bhattacharya J, Butte AJ. 2010. An environment-wide association study (EWAS) on type 2 diabetes mellitus. *PLoS ONE* 5(5):e10746.
- Pearson JF, Bachireddy C, Shyamprasad S, Goldfine AB, Brownstein JS. 2010. Association Between Fine Particulate Matter and Diabetes Prevalence in the U.S. *Diabetes Care* 33(10):2196-2201.
- Persky V, Piorkowski J, Turyk M, Freels S, Chatterton Jr R, Dimos J, et al. 2011. Associations of polychlorinated biphenyl exposure and endogenous hormones with diabetes in post-menopausal women previously employed at a capacitor manufacturing plant. *Environmental Research* 111(6):817-824.
- Piaggi S, Novelli M, Martino L, Masini M, Raggi C, Orciuolo E, et al. 2007. Cell death and impairment of glucose-stimulated insulin secretion induced by 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in the beta-cell line INS-1E. *Toxicol Appl Pharmacol* 220(3):333-340.
- Potter CL, Sipes IG, Russell DH. 1983. Hypothyroxinemia and hypothermia in rats in response to 2,3,7,8-tetrachlorodibenzo-p-dioxin administration. *Toxicology and applied pharmacology* 69(1):89-95.
- Rao MS, Subbarao V, Scarpelli DG. 1988. Development of hepatocytes in the pancreas of hamsters treated with 2,3,7,8-tetrachlorodibenzo-p-dioxin. *J Toxicol Environ Health* 25(2):201-205.
- Rignell-Hydbom A, Elfving M, Ivarsson SA, Lindh C, Jonsson BA, Olofsson P, et al. 2010. A nested case-control study of intrauterine exposure to persistent organochlorine pollutants in relation to risk of type 1 diabetes. *PloS one* 5(6):e11281.
- Rignell-Hydbom A, Lidfeldt J, Kiviranta H, Rantakokko P, Samsioe G, Agardh CD, et al. 2009. Exposure to p,p'-DDE: a risk factor for type 2 diabetes. *PLoS One* 4(10):e7503.
- Rozman K, Pereira D, Iatropoulos MJ. 1986. Histopathology of interscapular brown adipose tissue, thyroid, and pancreas in 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)-treated rats. *Toxicol Appl Pharmacol* 82(3):551-559.
- Ruzzin J, Petersen R, Meugnier E, Madsen L, Lock E-J, Lillefosse H, et al. 2010. Persistent organic pollutant exposure leads to insulin resistance syndrome. *Environ Health Perspect* 118(4):465-471.

- Shimba S, Wada T, Tezuka M. 2001. Arylhydrocarbon receptor (AhR) is involved in negative regulation of adipose differentiation in 3T3-L1 cells: AhR inhibits adipose differentiation independently of dioxin. *J Cell Sci* 114(Pt 15):2809-2817.
- Son HK, Kim SA, Kang JH, Chang YS, Park SK, Lee SK, et al. 2010. Strong associations between low-dose organochlorine pesticides and type 2 diabetes in Korea. *Environ Int* 36(5):410-414.
- Stahl BU, Beer DG, Weber LW, Lebofsky M, Rozman K. 1992. Decreased hepatic phosphoenolpyruvate carboxykinase gene expression after 2,3,7,8-tetrachlorodibenzo-p-dioxin treatment: implications for the acute toxicity of chlorinated dibenzo-p-dioxins in the rat. *Archives of toxicology Supplement = Archiv fur Toxikologie Supplement* 15:151-155.
- Steenland K, Calvert G, Ketchum N, Michalek J. 2001. Dioxin and diabetes mellitus: an analysis of the combined NIOSH and Ranch Hand data. *Occup Environ Med* 58(10):641-648.
- Sweeney MH, Calvert GM, Egeland GA, Fingerhut MA, Halperin WE, Piacitelli LA. 1997. Review and update of the results of the NIOSH medical study of workers exposed to chemicals contaminated with 2,3,7,8-tetrachlorodibenzodioxin. *Teratog Carcinog Mutagen* 17(4-5):241-247.
- Tabák AG, Herder C, Rathmann W, Brunner EJ, Kivimäki M. 2012. Prediabetes: a high-risk state for diabetes development. *The Lancet* 379(9833):2279-2290.
- Tang F, Yan C, Li F, Wu S, Yu Y, Gao Y, et al. 2007. Protective effects of insulin on polychlorinated biphenyls-induced disruption of actin cytoskeleton in hippocampal neurons. *Environ Toxicol* 22(2):152-158.
- Thayer KA, Heindel JJ, Bucher JR, Gallo MA. 2012. Role of environmental chemicals in diabetes and obesity: A National Toxicology Program workshop report. *Environ Health Perspect* 120(6):779-789.
- Turyk M, Anderson H, Knobeloch L, Imm P, Persky V. 2009a. Organochlorine exposure and incidence of diabetes in a cohort of Great Lakes sport fish consumers. *Environ Health Perspect* 117(7):1076-1082.
- Turyk M, Anderson HA, Knobeloch L, Imm P, Persky VW. 2009b. Prevalence of diabetes and body burdens of polychlorinated biphenyls, polybrominated diphenyl ethers, and p,p'-diphenyldichloroethene in Great Lakes sport fish consumers. *Chemosphere* 75(5):674-679.

- Uemura H, Arisawa K, Hiyoshi M, Satoh H, Sumiyoshi Y, Morinaga K, et al. 2008. Associations of environmental exposure to dioxins with prevalent diabetes among general inhabitants in Japan. *Environ Res* 108(1):63-68.
- Ukropec J, Radikova Z, Huckova M, Koska J, Kocan A, Sebkova E, et al. 2010. High prevalence of prediabetes and diabetes in a population exposed to high levels of an organochlorine cocktail. *Diabetologia* 53(5):899-906.
- Unkila M, Ruotsalainen M, Pohjanvirta R, Viluksela M, MacDonald E, Tuomisto JT, et al. 1995. Effect of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) on tryptophan and glucose homeostasis in the most TCDD-susceptible and the most TCDD-resistant species, guinea pigs and hamsters. *Arch Toxicol* 69(10):677-683.
- Vandenberg LN, Colborn T, Hayes TB, Heindel JJ, Jacobs DR, Jr., Lee DH, et al. 2012. Hormones and Endocrine-Disrupting Chemicals: Low-Dose Effects and Nonmonotonic Dose Responses. *Endocrine reviews*.
- Vasiliu O, Cameron L, Gardiner J, Deguire P, Karmaus W. 2006. Polybrominated biphenyls, polychlorinated biphenyls, body weight, and incidence of adult-onset diabetes mellitus. *Epidemiol* 17(4):352-359.
- Viluksela M, Stahl BU, Birnbaum LS, Rozman KK. 1998. Subchronic/chronic toxicity of a mixture of four chlorinated dibenzo-p-dioxins in rats. II. Biochemical effects. *Toxicol Appl Pharmacol* 151(1):70-78.
- Viluksela M, Unkila M, Pohjanvirta R, Tuomisto JT, Stahl BU, Rozman KK, et al. 1999. Effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) on liver phosphoenolpyruvate carboxykinase (PEPCK) activity, glucose homeostasis and plasma amino acid concentrations in the most TCDD-susceptible and the most TCDD-resistant rat strains. *Arch Toxicol* 73(6):323-336.
- Wang J, Lv X, Du Y. 2010. Inflammatory response and insulin signaling alteration induced by PCB77. *J Environ Sci (China)* 22(7):1086-1090.
- Wassermann D, Wassermann M, Lemesch C. 1975. Ultrastructure of beta-cells of the endocrine pancreas in rats receiving polychlorinated biphenyls. *Environ Physiol Biochem* 5(5):322-340.
- Weber LW, Haart TW, Rozman K. 1987. Effect of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) on thermogenesis in brown adipose tissue of rats. *Toxicol Lett* 39(2-3):241-248.

WHO. 2011. Global Burden of Disease Project: Diabetes Programme Facts and Figures.  
<http://www.who.int/diabetes/facts/en/> [accessed 12 December 2011].



## **Appendix 1. Data Gaps and Research Recommendations**

### Data Gaps:

- The effects of mixtures on POPs and other environmental chemicals
- High throughput surrogate exposure measures based on biological activity
- Longitudinal studies with repeated measurements of developmental exposures and outcomes (e.g., obesity, diabetes, and related metabolic disturbances) to follow progression of disease
- Relationships between POPs and T1D [only one prospective study (Rignell-Hydbom et al. 2010)]
- Studies on age, time period, and cohort effects of POPs exposure and incident diabetes
- Studies of Type 2 diabetes in non-overweight or obese.

### Research Recommendations:

- Promote collaboration between epidemiologists, clinicians, and laboratory scientists to work in a true translational way
- Epidemiological and animal studies of the progressive development of disease over time considering factors such as genetics, age, window of exposure, and lifestyle
- Better animal models of diabetes and obesity
- Studies should include measurement of glucose endpoints, lipid profiles, insulin resistance, waist circumference and other measures of obesity, and blood pressure
- Interaction between POP exposure and genotype concerning future T1D and T2D diabetes development
- Better understanding of non-monotonic relationships, i.e., frequency of occurrence and biological basis
- Focus on chemicals present in the population now for which the extent of exposure is expected to increase or stay the same.
- Consider differences in exposure across generations
- Consider the influence of subclinical disease on biomarkers of exposure

- Development of improved high-throughput assays to measure POPs in low blood volumes at a reasonable cost
- Use improved analytical measures on bio-banked blood from existing longitudinal studies
- Identify biological pathways for diabetes and related disease states and screen existing POPs for activity in these pathways in higher throughput assay systems

## Figure Legends

### **Figure 1. Associations between trans-nonachlor and diabetes in epidemiological studies.**

Abbreviations: CARDIA, Coronary Artery Risk Development in Young Adults Study; NHANES, National Health and Nutrition Examination Survey; HHANES, Health and Nutrition Examination Survey; CS, cross-sectional; NCC, nested case-control; FBG, fasting blood glucose; HbA1c, glycated hemoglobin; OR, odds ratio; Q, quartile; std, standardized; T, tertile; %ile, percentile; adj, adjusted. Self-report indicates a self-reported diagnosis of type 2 diabetes; meds refers to medications used to treat type 2 diabetes; FBG and HbA1c indicate levels that were sufficiently elevated to be classified as type 2 diabetes. <sup>a</sup>Values are adjusted ORs unless otherwise noted. <sup>b</sup>If no lipid adjustments were reported, the OR was not lipid adjusted; all exposures were measured in serum samples.

### **Figure 2. Association between DDE, DDT or DDD and diabetes in epidemiological studies.**

Abbreviations: CARDIA, Coronary Artery Risk Development in Young Adults Study; HHANES, Health and Nutrition Examination Survey; NHANES, National Health and Nutrition Examination Survey; CS, cross-sectional; FBG, fasting blood glucose; HbA1c glycated hemoglobin; IRR, incidence rate ratio; ND, not determined; OGTT, oral glucose tolerance test; %ile, percentile; adj, adjusted; Q, quantile; stand, standardized; T, tertile. Self report indicates self-reported diagnosis of type 2 diabetes; medication refers to medications used to treat type 2 diabetes; OGTT, FBG, and HbA1c indicate levels that were sufficiently elevated to be classified as type 2 diabetes. <sup>a</sup>Values are adjusted ORs unless otherwise noted. <sup>b</sup>If no lipid adjustments were reported, the OR was not lipid adjusted; all exposures were measured in serum samples.

**Figure 3. Association between PCBs and diabetes in epidemiological studies.** Abbreviations: CARDIA, Coronary Artery Risk Development in Young Adults Study; WHILA, Women's Health in the Lund Area; CS, cross-sectional; Pros, prospective; FBG, fasting blood glucose; HbA1c, glycated hemoglobin; IDR, incidence density ratio; IRR, incidence rate ratio; med, median; ND, not determined; OGTT, oral glucose tolerance test; Q, quantile; Std, standardized; %ile, percentile; adj, adjusted; T, tertile; SR indicates self-reported diagnosis of type 2 diabetes; meds refers to medications used to treat type 2 diabetes; OGTT, FBG, and HbA1c indicate levels that were sufficiently elevated to be classified as type 2 diabetes. <sup>a</sup>Values are adjusted ORs unless otherwise noted. <sup>b</sup>If no lipid adjustments were reported, the OR was not lipid adjusted; exposures were measured in serum samples unless otherwise indicated.

**Figure 4. Association between Agent Orange or dioxin and diabetes in studies of Vietnam veterans.** Abbreviations: AFHS [ORH], Air Force Health Study Operation Ranch Hand; adj, adjusted; FBG, fasting blood glucose; OGTT, oral glucose tolerance test; Phys. Dx, physician diagnosis; HR, hazard ratio; RR, relative risk; Q, quantile; OGTT, and FBG indicate levels that were sufficiently elevated to be classified as type 2 diabetes. <sup>a</sup>Values are adjusted ORs unless otherwise noted. <sup>b</sup>If no lipid adjustments were reported, the OR was not lipid adjusted

**Figure 5. Association between miscellaneous organochlorine POPs and diabetes in epidemiological studies.** Abbreviations: CARDIA, Coronary Artery Risk Development in Young Adults Study; NHANES, National Health and Nutrition Examination Survey; HHANES, Health and Nutrition Examination Survey; AFHS [ORH], Air Force Health Study [Operation Ranch Hand]; PIVUS, The Prospective Investigation of the vasculature in Uppsala Seniors Study; NCC, nested case-control; CS, cross-sectional; RR, relative risk; FBG, fasting blood glucose; HbA1c, glycated hemoglobin; OGTT, oral glucose tolerance test; meds, medication;

phys. dx, physician diagnosis; med exam, medical exam; ND, not determined; %ile, percentile; adj, adjusted; Q, quantile; T, tertile; SR indicates self-reported diagnosis of type 2 diabetes; meds refers to medications used to treat type 2 diabetes; OGTT, FBG, and HbA1c indicate levels that were sufficiently elevated to be classified as type 2 diabetes. <sup>a</sup>Values are adjusted ORs unless otherwise noted. <sup>b</sup>If no lipid adjustments were reported, the OR was not lipid adjusted; exposures were measured in serum samples unless otherwise indicated.

**Figure 6. Association between POPs mixtures and diabetes in epidemiological studies.**

Chemical (n): n refers to the number of chemicals included in the mixture assessment. Abbreviations: CARDIA, Coronary Artery Risk Development in Young Adults Study; NHANES, National Health and Nutrition Examination Survey; CC, case-control; CS, cross-sectional; IRR, incidence rate ratio; FBG, fasting blood glucose; HbA1c, glycated hemoglobin; OGTT, oral glucose tolerance test; %ile, percentile; adj, adjusted; Q, quantile; T, tertile; SR indicates self-reported diagnosis of type 2 diabetes; meds refers to medications used to treat type 2 diabetes; OGTT, FBG, and HbA1c indicate levels that were sufficiently elevated to be classified as type 2 diabetes. <sup>a</sup>Values are adjusted ORs unless otherwise noted. <sup>b</sup>If no lipid adjustments were reported, the OR was not lipid adjusted

**Figure 7. Association between brominated compounds and diabetes in epidemiological studies.**

Abbreviations: CARDIA, Coronary Artery Risk Development in Young Adults Study; NHANES, National Health and Nutrition Examination Survey; SR, self-report; CC, case-control; CS, cross-sectional; IDR, incidence density ratio; FBG, fasting blood glucose; HbA1c, glycated hemoglobin; ND, not determined; %ile, percentile; adj, adjusted; Q, quantile; SR indicates self-reported diagnosis of type 2 diabetes; meds refers to medications used to treat type 2 diabetes; FBG, and HbA1c indicate levels that were sufficiently elevated to be classified as type 2

diabetes. <sup>a</sup>Values are adjusted ORs unless otherwise noted. <sup>b</sup>If no lipid adjustments were reported, the OR was not lipid adjusted; all exposures were measured in serum samples.

**Figure 8. Association between PFAAs and diabetes in epidemiological studies.**

Abbreviations: C8 Health, C8 Health Project; NHANES, National Health and Nutrition Examination Survey; CS, cross-sectional; Q, quantile; SR indicates self-reported diagnosis of type 2 diabetes. <sup>a</sup>Values are adjusted ORs unless otherwise noted. <sup>b</sup>If no lipid adjustments were reported, the OR was not lipid adjusted; all exposures were measured in serum samples.

Reference	Study Description (n)	Outcome Assessment	adjOR (95% CI) <sup>a</sup>	Exposure Contrast <sup>b</sup>
Lee et al. 2010	USA (multisite), CARDIA; NCC, ≥ 18 years, ♂♀ (180)	FBG, meds	2.0 (0.6, 6.9)	Q4 vs. Q1 ng/g lipid adj.
Everett et al. 2010	USA, NHANES 1999-2004; CS. ≥ 20 years, ♂♀ (3,049)	Self-report, HbA1c	2.36 (1.48, 3.76)	≥14.5 vs. <14.5 ng/g lipid adj.
Lee et al. 2006	USA, NHANES 1999-2002; CS, ≥ 20 years, ♂♀ (658)	FBG, Self-report	2.5 (1, 6.1)	25 to <50th %ile vs. ND ng/g lipid adj.
Cox et al. 2007	USA, HHANES 1982-1984; CS, ≥ 20 years, ♂♀ (1,303)	Self-report	2.9 (1.3, 6.4)	≥1.0 vs. <1.0 ng/g wet weight
Son et al. 2010	South Korea, Uljin; CS, ≥ 40 years, ♂♀ (51)	FBG, meds	8.1 (1.2, 53.5)	T3 vs. T1 ng/g lipid std.

Legend: prospective or nested CC    cross-sectional

Figure 1.

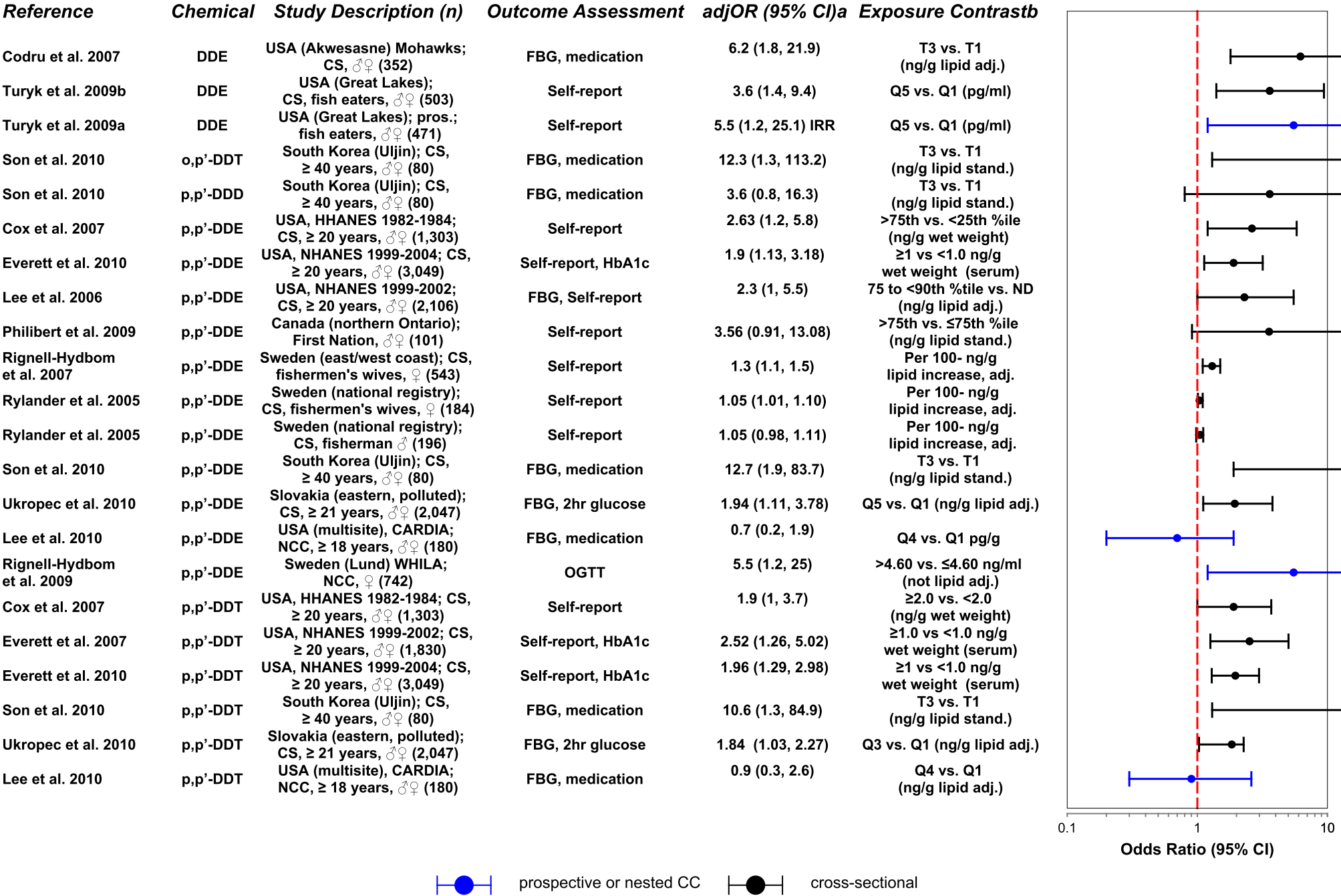


Figure 2.



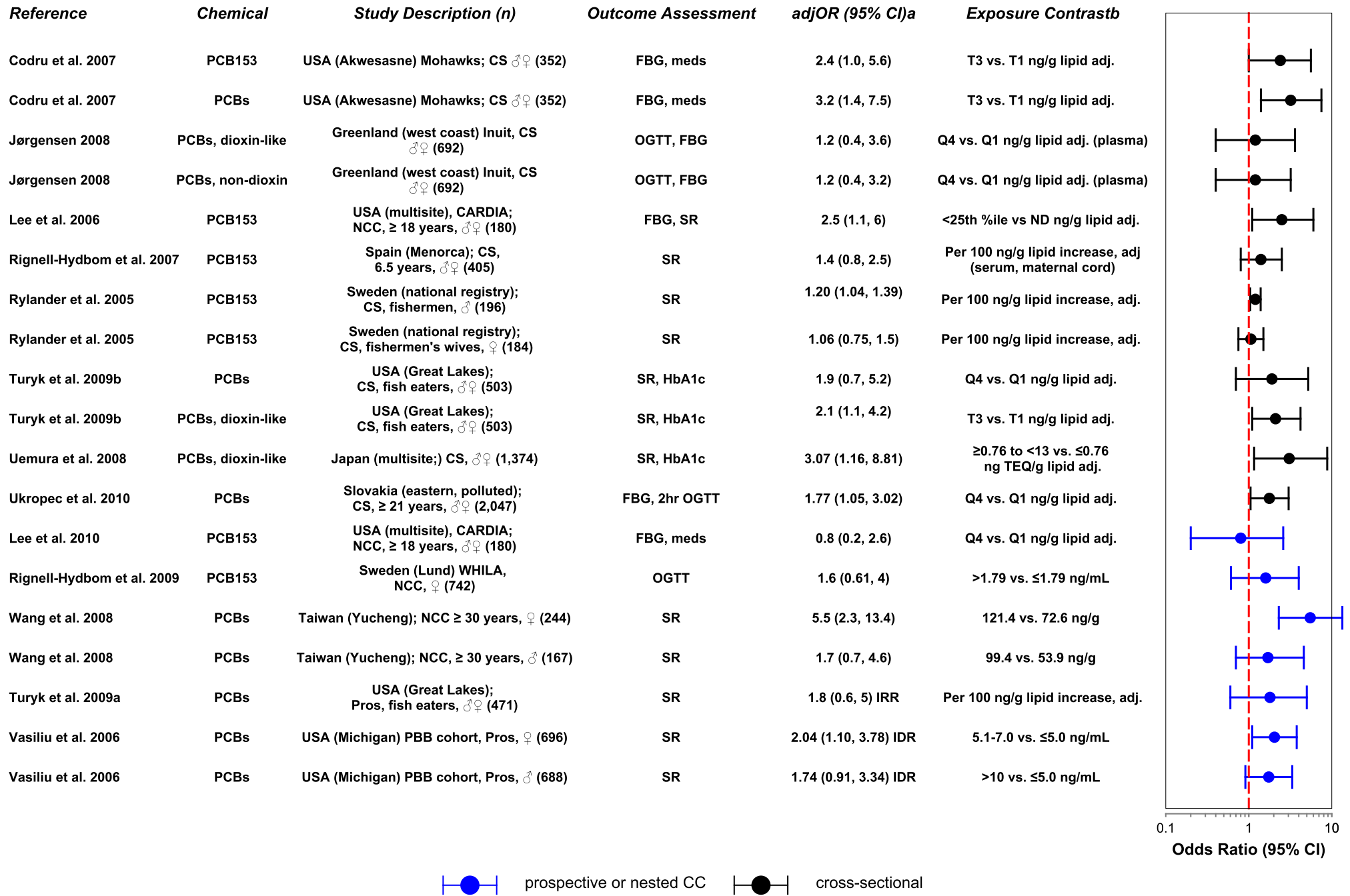


Figure 3.

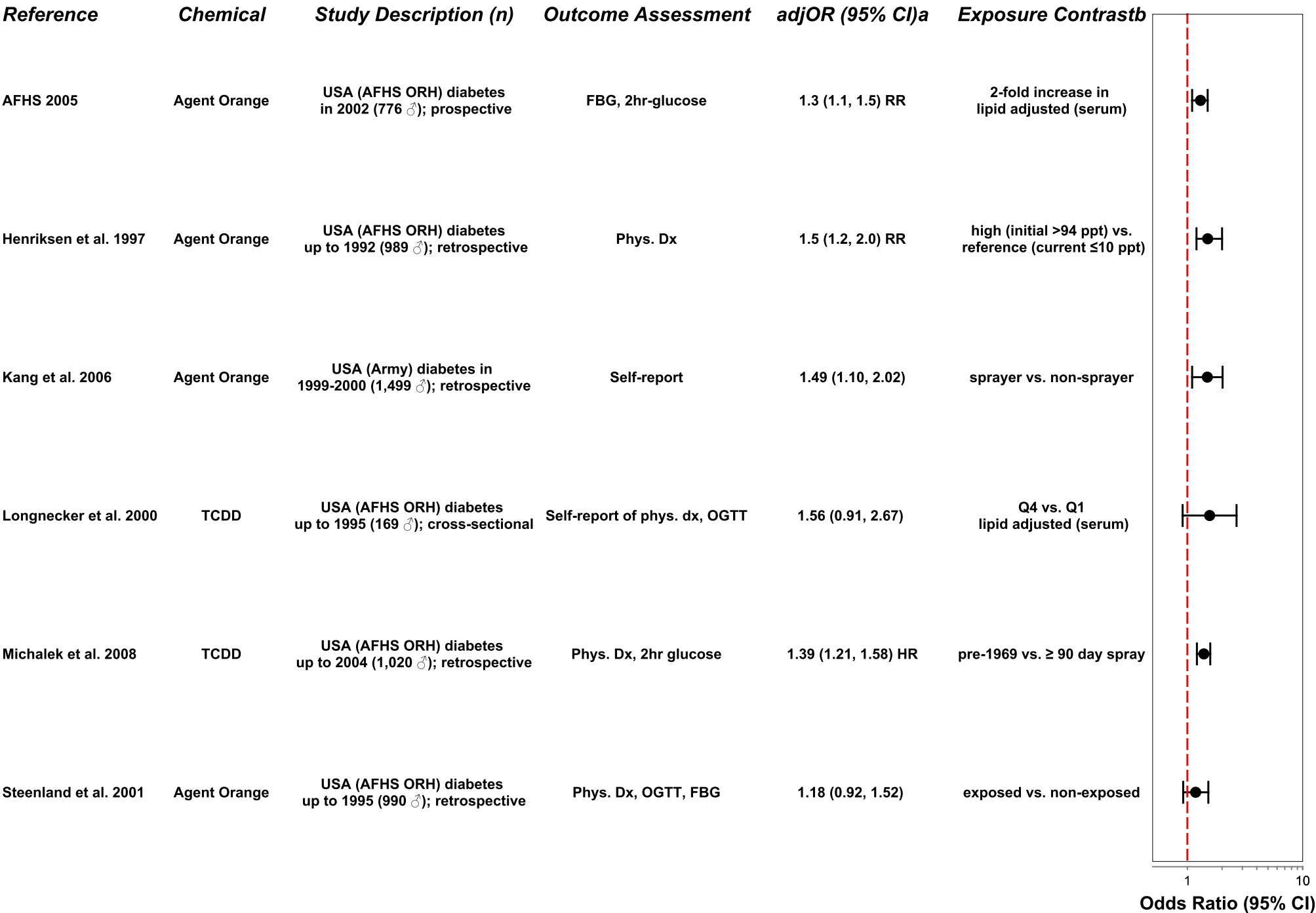


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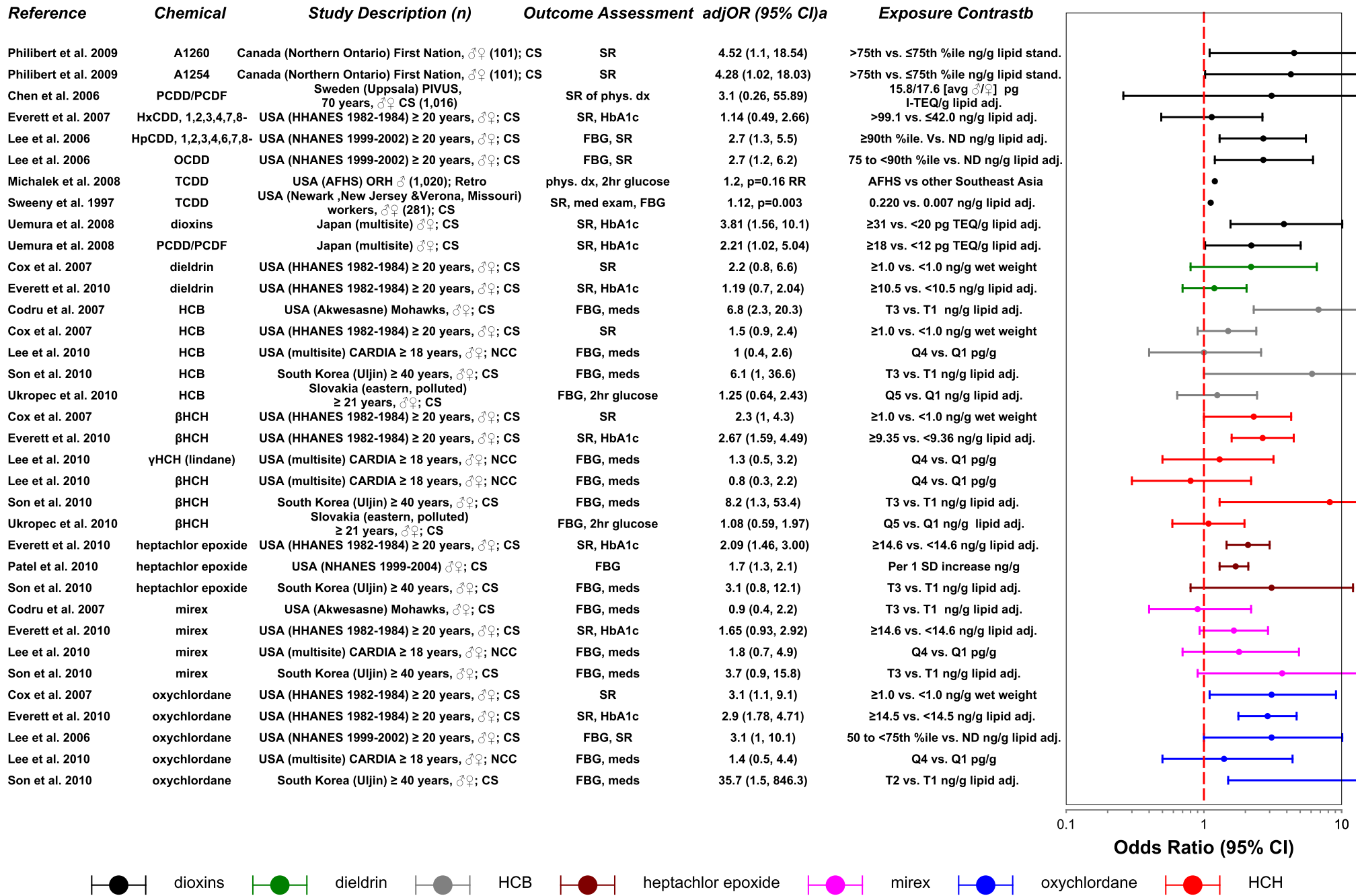


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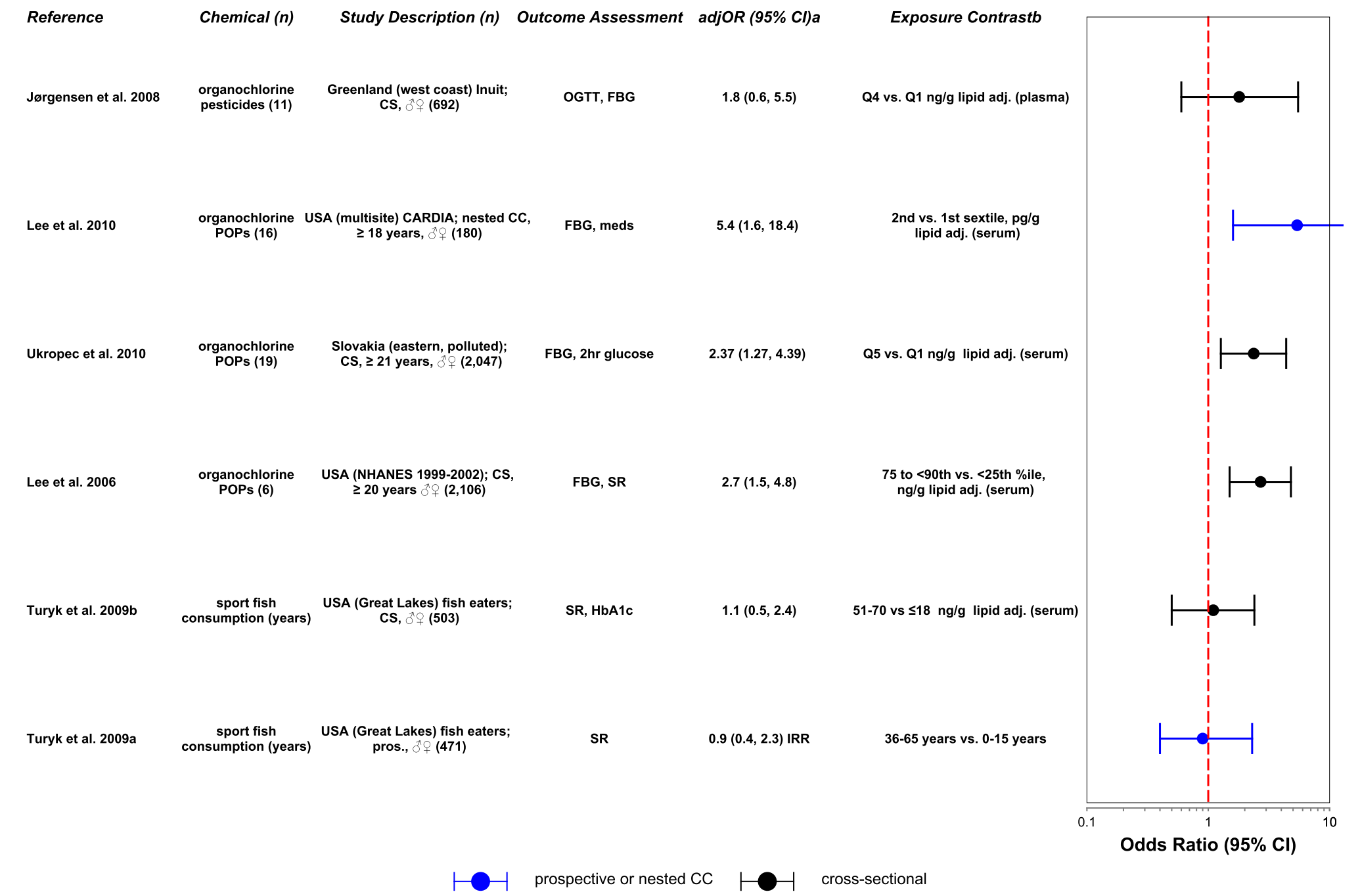


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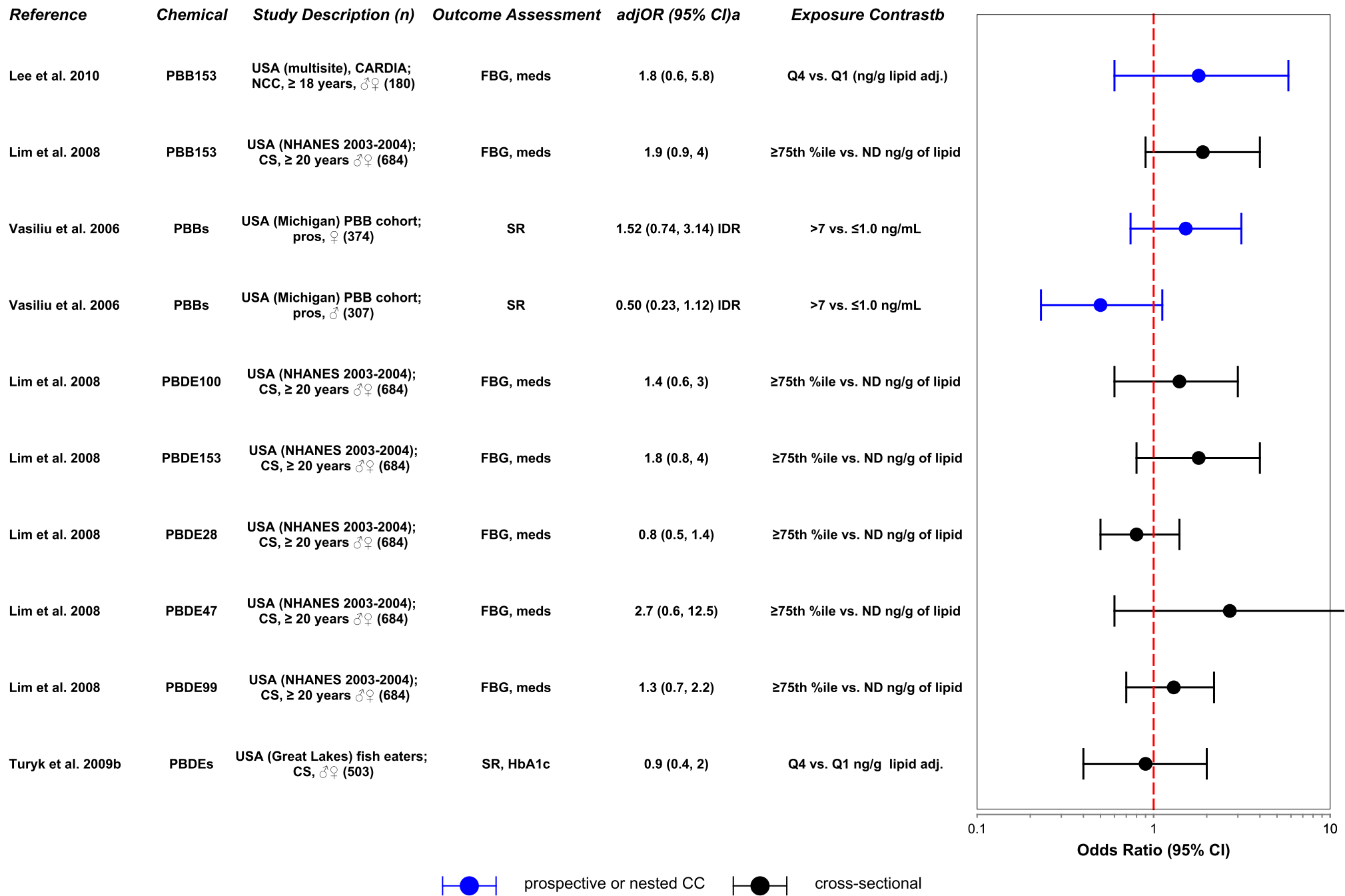


Figure 7.

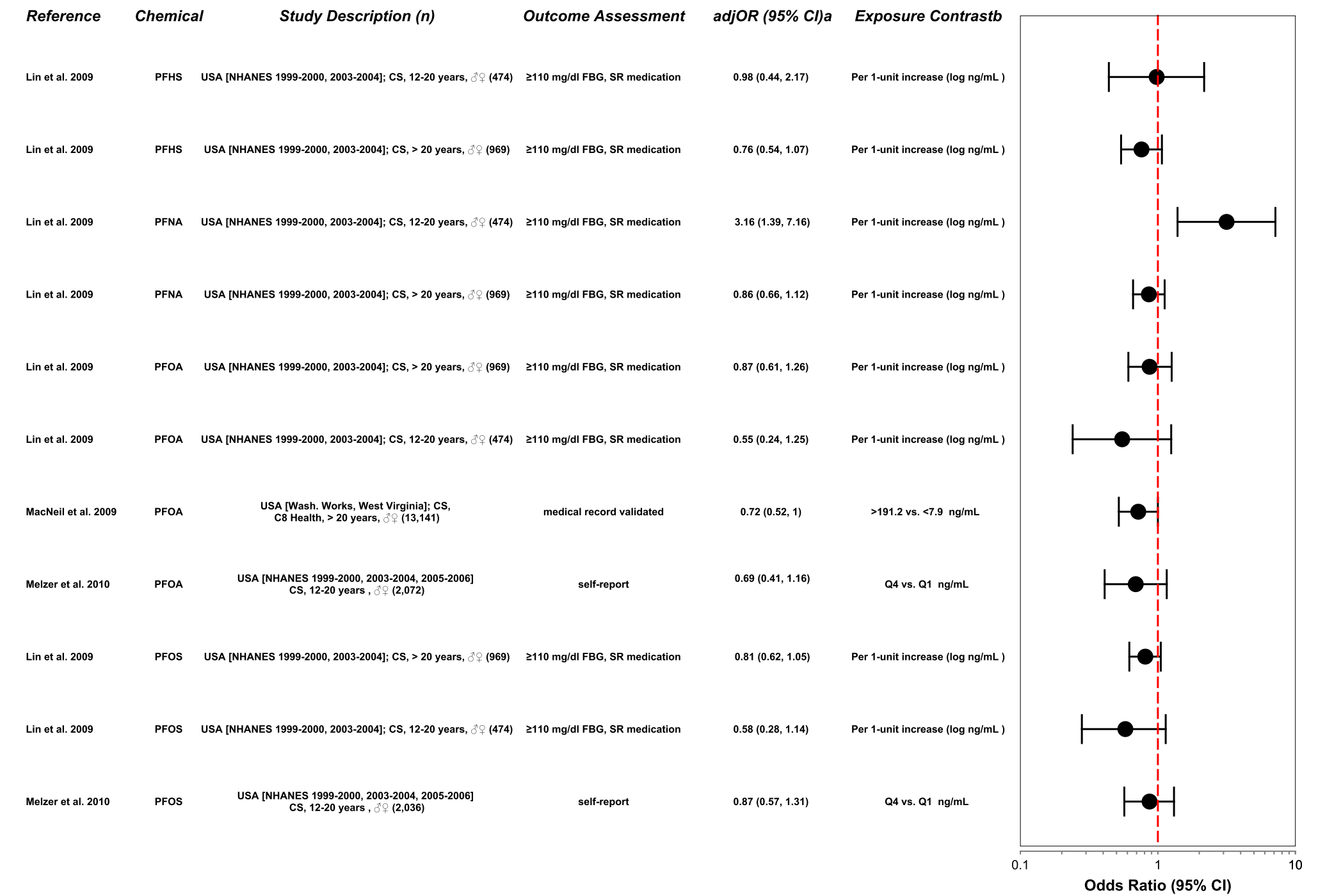


Figure 8.